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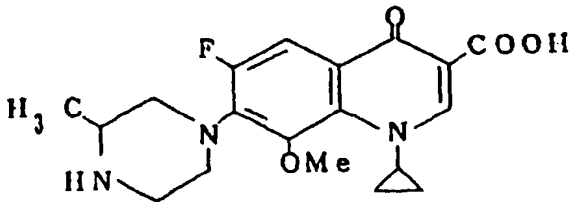
(54) 8-ALKOXYQUINOLONECARBOXYLIC ACID HYDRATE WITH EXCELLENT STABILITY AND PROCESS FOR PRODUCING THE SAME

(57) The invention provides 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate with excellent stability represented by a following formula (1),



(1)

• 3/2H2O

and process for producing the same.

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Description

Technical Field

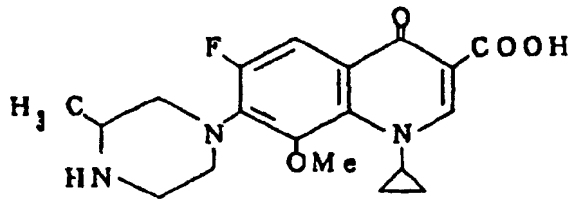
The present invention relates to 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate with excellent stability and process for producing the same.

Background Technology

Antibacterial agents of the quinolonecarboxylic acid class have achieved a striking progress in recent years. Because of broad antibacterial spectrum and potent bactericidal activity ranging from Gram-positive bacteria to negative bacteria, they have become to be used for surgical infectious diseases as well as urinary tract infectious disease and their usefulness is highly appreciated, leading to great contribution in the clinical practice.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid is particularly noted because of not only its potent antibacterial activity but also higher selectivity against bacteria from mammalian cells, which brings on an excellent selective toxicity.

In Japanese Unexamined Patent Publication No. Sho 62-252772, hemihydrate of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid represented by a formula (2) is disclosed.



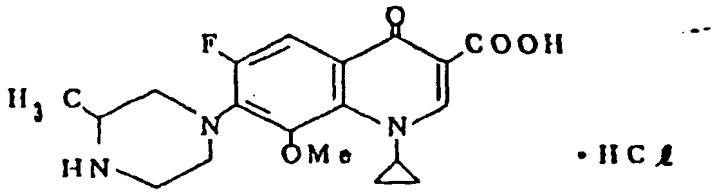
(2)

• 1/2H2O

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid tends to make a hydrate because of its strong hygroscopicity, and it easily forms a hemihydrate when recrystallizing from water-containing organic solvent or when drying crystals obtained by the recrystallisation method by neutralization according to acid-alkali recrystallisation.

It was revealed by us, however, that the measured weight of this hemihydrate increases with the rise of environmental humidity. It was further revealed by us that the tablet containing the hemihydrate has poor disintegration and dissolution rates, leading to disadvantages in pharmaceutical manufacturing.

Moreover, in Japanese Unexamined Patent Publication No. Sho 63-198664, hydrochloride of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid represented by a formula (3) is disclosed.



(3)

• HCl

However, with respect to this hydrochloride (3), too, the instability due to the hygroscopicity of drug substance same as or more than that of hemihydrate (2) and the problems of poor disintegration and dissolution rate when converted to tablets have become evident.

Disclosure of the Invention.

As a result of studies for the purpose of solving the problems of said 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid hemihydrate and hydrochlorlde, the inventors have found that 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesqui-

hydrate is a stable compound and excellent also in pharmaceutical manufacturing. Namely, 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate has been found to be stable under different conditions of humidity, and the disintegration and dissolution rates of the tablets manufactured have also found to be good.

In addition, as a means to obtain 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate, we have found that the target compound can be obtained efficiently by heating an aqueous suspension of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid under stirring, leading to the completion of the invention.

Here, the aqueous suspension represents a suspension after neutralization in the acid-alkali recrystallization during the process for purification, a suspension of isolated crystals added with water, or the like, and it is possible to manipulate with amount of water 3 to 20 times as much as crystals, but it is preferable to use 3 to 5 times for obtaining the target compound in high yield.

It is optimum to stir for 10 to 30 minutes at a temperature of, for example, 50 to 100 °C, preferably 80 to 90 °C.

The pH of aqueous suspension is preferable to be in the vicinity of neutrality (6.0 - 8.0).

After collecting the first crop of the target compound by filtration, the second crop can be obtained by cooling the filtrate to room temperature, which may result in an increase of overall yield.

Brief Description of the Drawings

Fig. 1 is a diagram showing the result of thermal analysis of the inventive substance, Fig. 2 is a diagram showing the result of thermal analysis of comparative substance, Fig. 3 is a diagram showing infrared spectrum of the inventive substance, Fig. 4 is a diagram showing infrared spectrum of comparative substance, Fig. 5 is a diagram showing the result of X-ray diffraction of the inventive substance, Fig. 6 is a diagram showing the result of X-ray diffraction of comparative substance, and Fig. 7 is an illustrative diagram showing the crystal structure of the inventive substance.

Best Embodiment for putting the Invention into Practice

In following, the invention will be illustrated in more detail showing an example, but the invention is not subject to any restriction by this example.

(Example 1)

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid (85 g) was suspended into water (425 ml, 5 times volume) and stirred for 10 minutes at an inner temperature of 80 to 85 °C. After hot filtration at the same temperature, the crystals were dried to obtain the target compound (84.43 g) at a yield of 92.7 %.

Elemental analysis: $C_{19}H_{22}FN_3O_4 \cdot 3/2H_2O$				
	C	H	N	Water content
Calculated	56.71	6.26	10.44	6.7
Found	56.79	6.15	10.44	7.3

(1) Instruments used

TG/DTA :	Rigaku Corporation (TAS-200; Control section), TG8101D2 (Measuring apparatus)
Infrared spectrophotometer :	Hitachi, Ltd., Model 270-30
Powder X-ray diffraction apparatus:	Rigaku Corporation, Model 2013
Single crystal X-ray diffraction apparatus :	Rigaku Corporation Model AFC5R
Karl Fischer moisture meter:	Kyoto Electronics Manufacturing Co., Ltd., Model MKA-3P

1) Thermal analysis (TG/DTA)

Employing each about 10 mg of samples of the inventive substance and comparative untreated substance without

hot water treatment, heating was performed from room temperature to 240 °C at a temperature-raising velocity of 5 °C/min, using α-alumina as a reference, and the gravimetric behavior and the thermal behavior at that time were measured, respectively. The results are shown in Fig. 1 for the inventive substance and in Fig. 2 for the comparative substance.

2) Infrared absorption spectrometry

Each sample of the inventive substance and untreated substance without hot water treatment was measured by KBr-transmission method. The results are shown in Fig. 3 for the inventive substance and in Fig. 4 for the comparative substance, respectively.

3) Powder X-ray diffraction

Each sample of the inventive substance and comparative substance was pulverized and measured using a glass sample plate. The results are shown in Fig. 5 for the inventive substance and in Fig. 6 for the comparative substance, respectively.

4) Single crystal X-ray diffraction

The crystal structure obtained as a result of X-ray diffraction is shown in Fig. 7.

1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate retained a constant amount of water under ordinary preservation conditions and was stable.

When comparing the measurement data of thermal analysis (TG/DTA), infrared absorption spectrometry and powder X-ray diffraction between the untreated substance and the inventive hot water-treated substance, the patterns differ obviously, hence it has become clear that the hot water-treated substance and the untreated substance have different crystal forms.

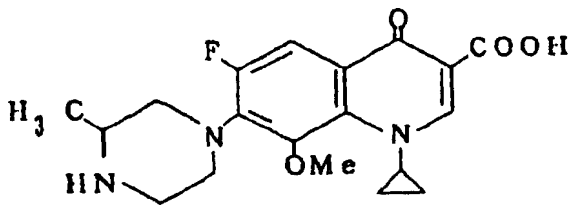
In addition, from the result of single crystal X-ray diffraction, it has been proved that 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate contains 8 molecules of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid and 12 molecules of water in a unit cell.

Utilizability in the industry

The inventive 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate is excellent in the disintegration and dissolution rate and stable, hence it is very useful for pharmaceutical manufacturing.

Claims

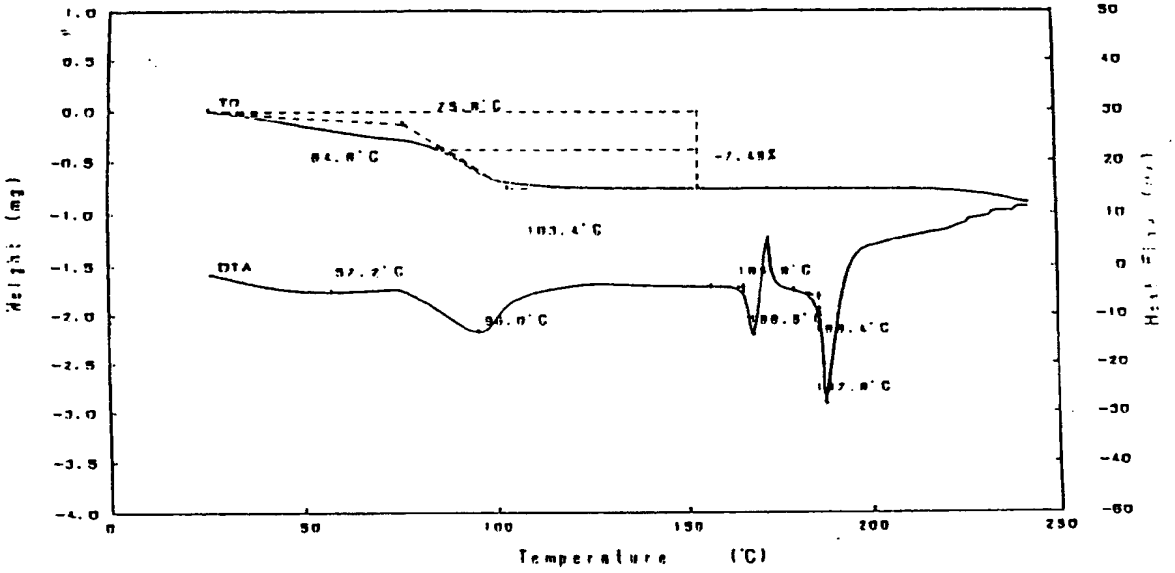
1. 1-Cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid sesquihydrate represented by a formula (1).



$\cdot\ 3/2H_2O$ (1)

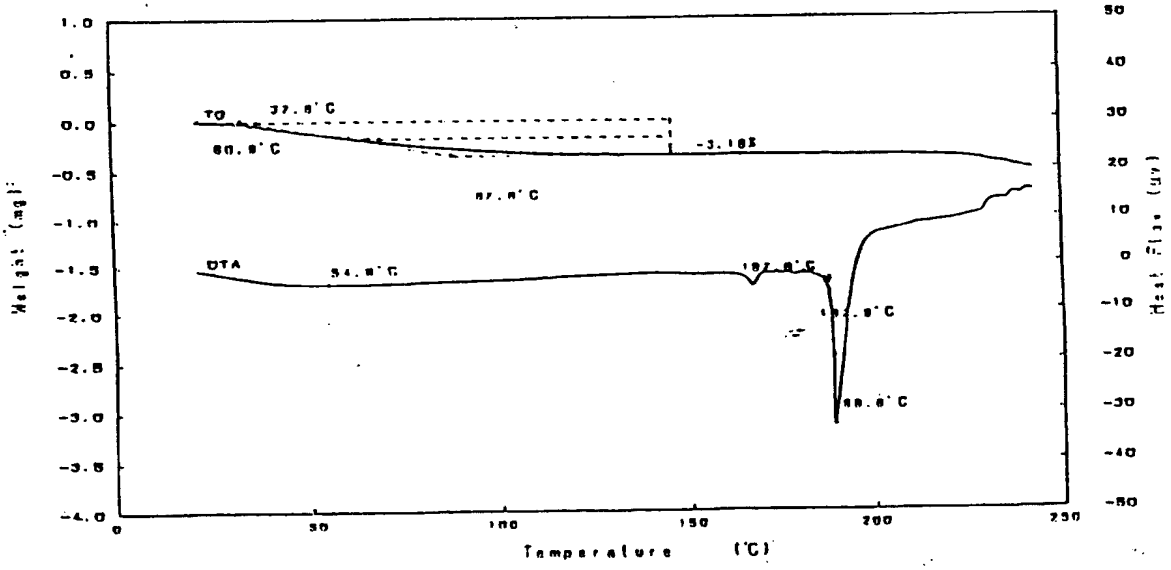
2. A process for producing the compound of Claim 1, characterized in that aqueous suspension of 1-cyclopropyl-6-fluoro-1,4-dihydro-8-methoxy-7-(3-methyl-1-piperazinyl)-4-oxo-3-quinolinecarboxylic acid is treated by heating under stirring.

Fig. 1



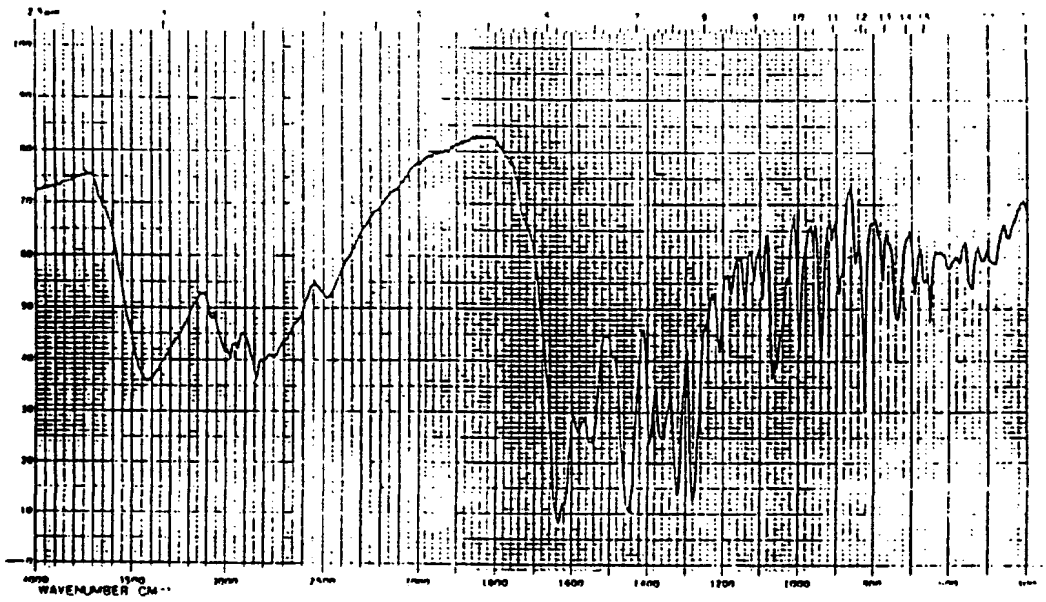
Hot water-treated substance

Fig. 2



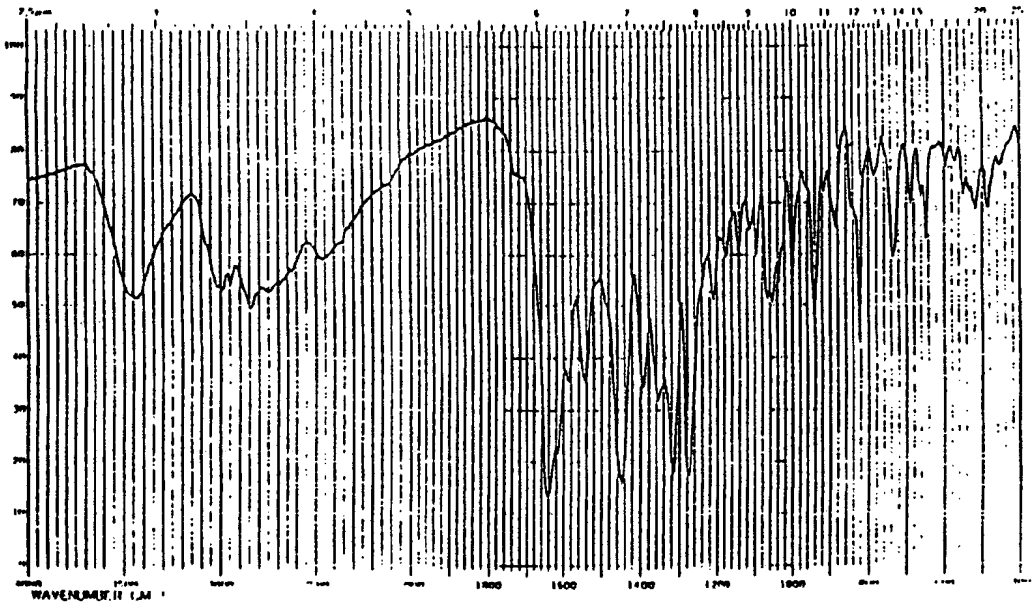
Untreated substance

Fig. 3



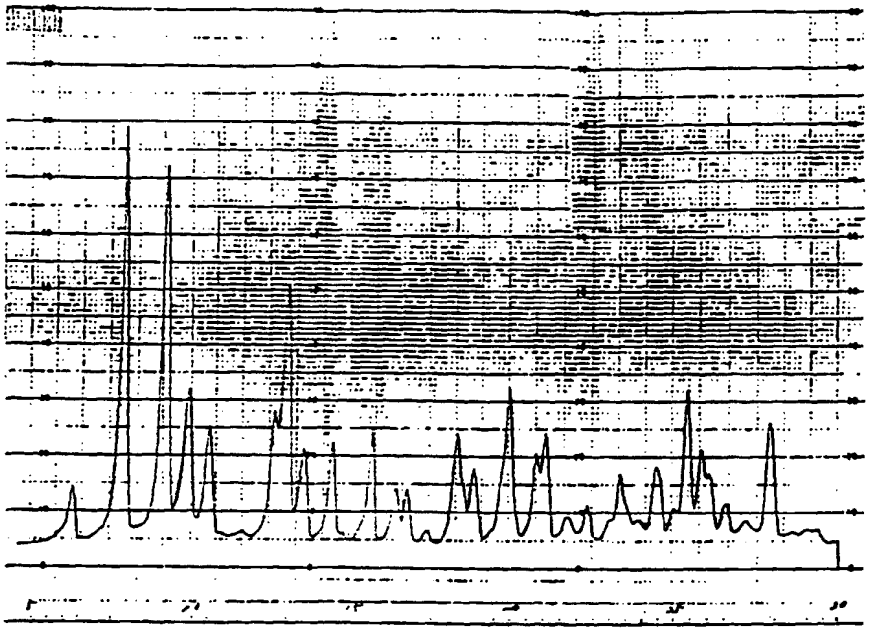
Hot water-treated substance

Fig. 4



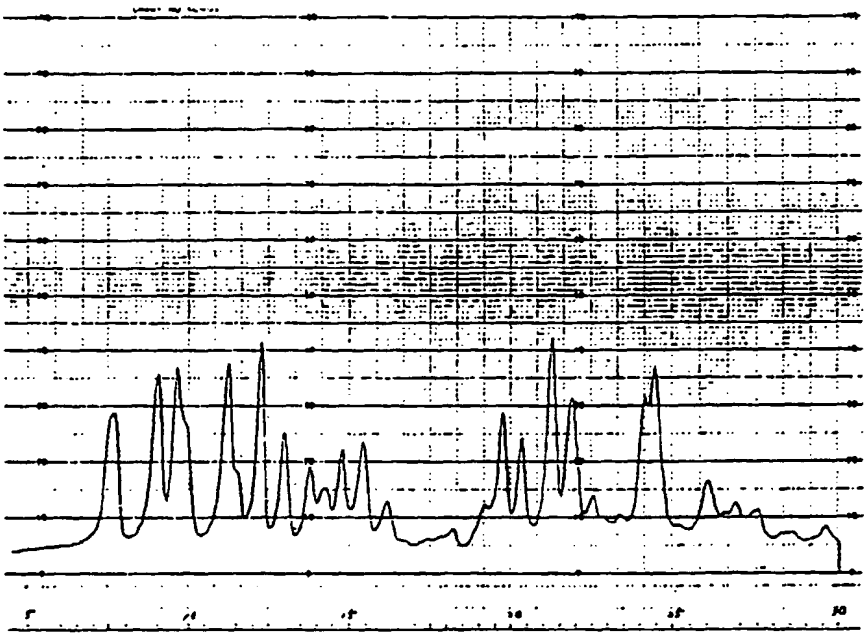
Untreated substance

Fig. 5



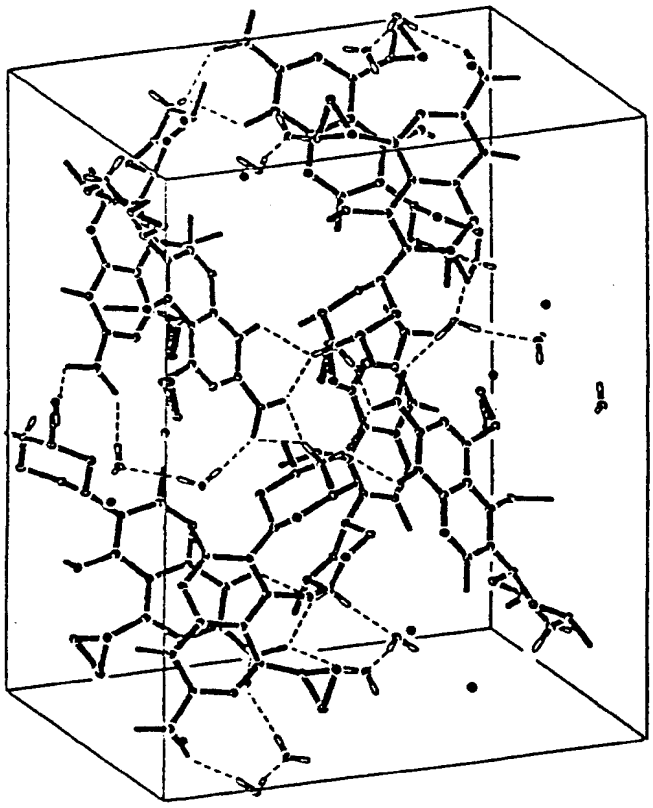
Hot water-treated substance

Fig. 6



Untreated substance

Fig. 7



INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP95/02477

A. CLASSIFICATION OF SUBJECT MATTER
Int. Cl^6 C07D401/04//A61K31/495
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED
Minimum documentation searched (classification system followed by classification symbols)
Int. Cl^6 C07D401/04, A61K31/495

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP, 62-252772, A (Kyorin Pharmaceutical Co., Ltd.), November 4, 1987 (04. 11. 87) & US, 4980470, A & EP, 230295, A	1, 2
X	JP, 63-198664, A (Sankyo Co., Ltd. and another), August 17, 1988 (17. 08. 88)(Family: none)	1, 2
Y	JP, 62-205060, A (Kyorin Pharmaceutical Co., Ltd.), September 9, 1987 (09. 09. 87) & EP, 235762, A	1, 2

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
January 24, 1996 (24. 01. 96)	February 6, 1996 (06. 02. 96)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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